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Original article

Pregnant women's knowledge and clinical management of hemolytic disease of the fetus and newborn in Pará, Brazil

Jhemily de Nazaré Gonçalves e Silva [a], *Andrya Maia de Souza* [b], *Fabiane Monteiro do Rosario* [b], *Laine Celestino Pinto* [b,c,*]

[a] *Imumunogenetics Laboratory, Federal University of Pará, Biological Science Institute, Belém, Pará, Brazil*
[b] *Department of Biomedicine, Centro Universitário Metropolitano da Amazônia, Belém, Pará, Brazil*
[c] *Laboratory of Experimental Neuropathology, Federal University of Pará, Biological Science Institute, Belém, Pará, Brazil*

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ABSTRACT

Objective: To evaluate the knowledge of pregnant women and the clinical management of hemolytic disease of the fetus and newborn, as well as to describe the gestational profile, risk factors and socio-epidemiological profile of pregnant women treated at two municipal health units in Belém (Pará, Brazil).

Methods: This was a cross-sectional analytical study, which consisted in the application of questionnaires to pregnant women who underwent prenatal care at the municipal health units.

Results: A total of 104 pregnant women were evaluated; most were aged between 24 and 29 years old, had high school degrees (38 %), family incomes between 1 and 2 minimum wages (45 %) and blood type O+ (43 %). Regarding the gestational profile, the participants were predominantly in the third trimester of pregnancy (49 %), started prenatal care in the first gestational trimester (81 %) and were primiparous (61 %). Failures in the management of prenatal care were observed, especially with regard to access to information about the disease, since most pregnant women did not receive information about blood incompatibility during prenatal care. This led to limited knowledge about the pathology of the disease evidenced by the fact that most of the correct answers were between Questions 0–4, which were significantly associated with the women's education and income.

Conclusions: Although hemolytic disease of the fetus and newborn is serious, the pregnant women in this study demonstrated little knowledge about the disease and had inadequate care by health professionals, reinforcing the importance of improving care for women's health and prenatal care.

* Corresponding author at: Centro Universitário Metropolitano da Amazônia; 72, Visconde de Souza Franco Avenue, Reduto, Belém, Pará, Brazil.
E-mail address: laine@famaz.edu.br (L.C. Pinto).

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Introduction

Hemolytic disease of the fetus and newborn (HDFN) is a pathology of immunological origin, mainly due to incompatibility between the ABO and Rhesus (Rh) blood groups of the mother and the fetus and a previous sensitization. In HDFN, immunoglobulin G (IgG) developed by the mother crosses the placental barrier and binds to fetal erythrocyte antigens, causing a process of hemolysis, anemia and other mild to severe complications.[1-3]

This disease is the most common cause of hemolytic anemia and hyperbilirubinemia in newborns and can lead to recurrent miscarriages, stillbirths and hydrops fetalis, depending on the severity. The cases that progress to the most severe forms are related to incompatibility of the Rh(D) blood system, which occurs between a woman who is Rh(D) negative and her fetus who is Rh(D) positive. In this case, maternal sensitization may occur due to blood transfusion or during a previous pregnancy of an Rh(D) positive fetus, which induces the formation of antibodies in the maternal circulation.[4,5]

Regarding blood systems associated with HDFN, ABO incompatibility affects 15–25 % of all pregnancies, however, only 1 % of individuals develop the condition. The response caused by ABO incompatibility is modest, probably due to the expression of ABO blood type antigens and their presentation in various organs.[1,6] On the other hand, the antibodies that cause severe HDFN are mainly anti-Rh(D) and less frequently anti-Kell (anti-K1) and anti-Rh(c).[5]

Although the introduction of immunoprophylaxis with anti-D immunoglobulin has contributed to a significant decrease in the incidence of HDFN caused by anti-D, this pathology is still a cause of fetal mortality and morbidity around the world.[7,8] Such cases may be associated with failures in the application of prophylaxis protocols, including late administration, incorrect dosage, and inappropriate use in RhD-positive or alloimmunized patients and in mothers with RhD-negative newborns, as well as errors in handling and storing immunoglobulin.[9]

Therefore, the adequate management of HDFN should start during the first prenatal appointment by performing ABO and Rh blood typing. In cases in which the father is Rh positive and the mother is Rh negative, an antibody screening should be requested in the first visit and monthly after 24 weeks in order to detect anti-erythrocyte antibodies.[10,11] From the antibody screening result, the best conduct for the pregnant woman is defined, which in cases of risk of HDFN will be the recommendation to administer anti-D immunoglobulin.[12]

In Brazil, studies that assess the level of knowledge of pregnant women regarding HDFN are limited and suggest that this is still an unknown disease.[13] Thus, our study aimed to evaluate the knowledge of pregnant women and the clinical management of HDFN, as well as to describe the gestational profile, associated risk factors and socio-epidemiological profile of pregnant women in two municipal health units in Belém (Pará, Brazil).

Methods

This was a cross-sectional analytical study, which occurred from September 2022 to October 2022 in two municipal health units in the city of Belém, Pará, Brazil, with a population sample based on convenience sampling. This study was carried out after approval by the Research Ethics Committee (CEP) of the Centro Universitário Metropolitano da Amazônia (UNIFAMAZ) under protocol CAAE 62,108,822.5.0000.5701.

As inclusion criteria, literate pregnant women (over age or under age) who performed prenatal care in the units were included. As exclusion criteria, those who were in the first prenatal appointment of the first pregnancy were excluded, due to the infeasibility of evaluating the clinical management of the disease; thus, 104 participants were selected.

The questionnaire was developed in easy-to-understand language and asked about socio-epidemiological data; gestational profile; risk factors related to HDFN and clinical management of HDFN. To assess knowledge about HDFN, eight specific questions on the questionnaire addressed information about HDFN regardless of prenatal care, the relationship between the disease and blood incompatibility, the purpose of the vaccine and who should take it, as well as the causes of the disease. The correct answers of Questions 1–4 and 8 are 'Yes' whereas the correct alternatives for Questions 5–7 are 'No'.

The questionnaires were individually presented to eight professionals with experience in the health field for content validation and clarity before they were applied to the pregnant women. This analysis aimed to verify whether all items were compatible with the study population (semantic analysis) and whether the presentation of the items was adequate (content analysis). For this, each question was evaluated using a scale from 1 to 10; questions were categorized as confusing (1 to 4), unclear (5 to 7) and clear (8 to 10). In addition, for each question there was a space for suggestions about improving the content and semantics. The clarity index was obtained through the arithmetic mean of the scores assigned by the professionals.[14]

In the validation stage of the questionnaire, questions referring to the gestational profile, HDFN risk factors and clinical management of HDFN obtained a clarity index between 8 and 10, and therefore were considered clear by health professionals with no need for changes. On the other hand, some questions regarding knowledge of HDFN had a clarity index of less than 7 and needed to be improved. Statements considered confusing by the evaluators were replaced by other terms with the same meaning and even some examples were included as suggested, so that the structure of the questionnaire was not significantly altered. After that, the questionnaire was resubmitted to the same professionals in order to verify the new version.

In addition, five pregnant women were selected to participate in a pilot test in order to analyze the effectiveness of the questionnaire. The test showed the need for changes in the sequence of specific questions about HDFN and the inclusion of a question about the beginning of prenatal care to analyze the exclusion criteria, because women in the first pregnancy and first prenatal appointment had not received information related to their management.

The data obtained were submitted to descriptive statistical analysis calculating frequencies using the Bioestat 5.0 software. Furthermore, the chi-square test ($\chi 2$) and the G test were used to verify any statistically significant differences

between the socio-epidemiological data, the gestational profile and the number of correct answers about the disease. For applied tests, only p-values <0.05 were considered statistically significant.

Results

A total of 104 pregnant women agreed to participate in this study within the established data collection period and four refused to participate. The five pilot test participants are not included in these figures. From the analysis of socio-epidemiological data, there was a higher frequency of pregnant women aged 24 to 29 years (31 %), the majority had high school degrees (38 %) and the most prevalent family incomes were between 1 and 2 minimum wages corresponding to 45 % of the interviewees (Table 1).

Regarding the gestational profile, there was a predominance of pregnant women (49 %) in the third trimester of pregnancy, the majority started prenatal care in the first gestational trimester (81 %) and reported being primiparous (61 %).

Among the risk factors for HDFN, the commonest detected blood type among the participants was O+, (43 %); the majority (51 %) reported not knowing the blood type of the biological father. In addition, most of the pregnant women (93 %) did not present blood transfusion as a risk factor.

With regard to the clinical management of HDFN during pregnancy, the study revealed that 77 % of the participants performed blood typing during pregnancy. The questions about receiving the anti-D vaccine in previous pregnancies and the period of administration of the vaccine did not apply to these pregnant women in 61 % and 97 % of the cases, respectively, since the majority were primiparous and Rh positive. The same was true about undergoing antibody screening during prenatal care, which did not apply to 93 % of participants as they did not have the negative Rh factor. Finally, 87 % of pregnant women claimed not to have received information about blood incompatibility during prenatal care (Table 1).

Based on these results, the pregnant women were divided into two groups; those who correctly answering between 0 and 4 questions and thus have limited knowledge on the subject, and those who answered between 5 and 8 questions correctly and thus had satisfactory prior knowledge about the disease.

Hence, the pregnant women's knowledge about the HDFN proved to be poor, since 87.5 % (91/104) correctly marked between 0 and 4 questions, while only 12.5 % (13/104) correctly answered between 5 and 8 questions. Most (73 %) reported that they had not read or heard any information about HDFN regardless of prenatal care, but the largest portion knew that the disease is related to blood incompatibility and that the newborn may have a different blood type than the mother (55 % and 53 %, respectively). Regarding vaccination, most of the women surveyed (88 %) did not know the purpose of the anti-D vaccine, 48 % stated that if the newborn were Rh negative, they would need the anti-D vaccine and 64 % believed that the mother and the newborn should receive the anti-D vaccine. Furthermore, when asked about

Table 1 – Socio-epidemiological characteristics, gestational profile, risk factors and clinical management of hemolytic disease of the fetus and newborn in pregnant women receiving care at two municipal health units in Belém, Pará, Brazil.

Variable	n	%
Socio-epidemiological		
Age group		
<18 years old	3	3
18–23 years old	27	26
24–29 years old	32	31
30–35 years old	25	24
>36 years old	17	16
Level of education		
Incomplete and complete primary education	5	5
Incomplete high school education	11	11
Complete high school education	40	38
Incomplete higher education	15	14
Complete higher education	33	32
Family income		
<1 minimum wage	34	33
Between 1 and 2 minimum wages	47	45
>2 minimum wages	23	22
Gestational profile		
Gestational age		
First trimester (1–12 weeks)	15	14
Second trimester (13–26 weeks)	38	37
Third trimester (27–40 weeks)	51	49
Start of prenatal care		
First trimester (1–12 weeks)	84	81
Second trimester (13–26 weeks)	19	18
Third trimester (27–40 weeks)	1	1
Number of pregnancies		
Primiparous	63	61
Multiparous	41	39
Risk factors related to HDFN		
Pregnant woman's blood type		
A+	25	24
B+	11	11
AB+	3	3
O+	45	43
O-	4	4
Do not know	16	15
Biological father's blood type		
A+	13	12
B+	4	4
AB+	1	1
O+	27	26
B-	2	2
O-	4	4
Do not know	53	51
Have you ever had a blood transfusion?		
Yes	14	13
No	90	87
Clinical management of HDFN		
Have you received information about blood incompatibility during pregnancy?		
Yes	14	13
No	90	87
Did you perform blood typing during pregnancy?		
Yes	80	77
No	23	22
Do not know	1	1
Did you perform antibody screening?		
Yes	1	1
No	6	6
Do not know	97	93

Table 1 (*continued*)

Variable	n	%
Did you receive anti-D vaccine in previous pregnancies?		
Yes	2	2
No	39	37
Do not know	63	61
When did you receive vaccine?		
During pregnancy	–	–
After pregnancy	2	2
Not applicable	101	97
Do not know	1	1

the occurrence of the disease in newborns with Rh negative blood type, regardless of the mother's blood type and the susceptibility to developing the disease in mothers with Rh negative blood type, 48 % could not answer both questions (Table 2).

On analyzing the number of correct answers of the pregnant women associated with the variables 'level of education' and 'family income', it was found that most of the pregnant women who correctly answered only between 0 and 4 questions had completed high school (41 %) and their family income was between 1 and 2 minimum wages (50 %). On the other hand, among those who correctly answered between 5 and 8 questions, there was a predominance of complete higher education (69 %) and family income >2 minimum wages (77 %). The results showed a significant association between the number of correctly answered questions with level of education (p-value = 0.0456) and family income (p-value <0.0001). There was no statistically significant difference in the age group, gestational age or number of pregnancies in relation to the number of correct answers (Table 3).

Table 2 – Assessment of knowledge about hemolytic disease of the fetus and newborn in pregnant women receiving care at two municipal health units in Belém, Pará, Brazil.

Questions	n	%
Have you read/heard any information about HDFN (regardless of prenatal care)?		
Yes	28	27
No	76	73
Is the disease related to incompatibility?		
Yes	57	55
No	13	12
I don't know	34	33
Can the newborn have a different blood type from the mother?		
Yes	55	53
No	35	34
I don't know	14	13
Do you know what the anti-D vaccine is for?		
Yes	13	12
No	91	88
If the newborn is negative, will he need the anti-D vaccine?		
Yes	50	48
No	16	15
I do not know	38	37
Should the mother and newborn receive the vaccine?		
Yes	66	64
No	19	18
I do not know	19	18
If the newborn is Rh negative, can the disease occur regardless of the mother's blood type?		
Yes	25	24
No	29	28
I do not know	50	48
Can pregnant women with negative blood type develop the disease?		
Yes	43	41
No	11	11
I do not know	50	48

Discussion

HDFN is still considered a public health problem around the world despite the existence of RhD immunoprophylaxis. These cases may be related to inadequacies in clinical management, hence reflecting the lack of knowledge about the disease among pregnant women and health professionals.[5,13,15] Moreover, access to prophylaxis is still low for sensitized women in low-income countries, thus making it a risk for Rh(D) negative women.[16]

The present study revealed that the pregnant women receiving care in Belém, Pará had failures in prenatal guidance, especially with regard to access to information about the disease, since most pregnant women did not receive information about incompatibility blood tests during prenatal care. This may be attributed to the fact that the most frequent blood type among the investigated women was O+.

In HDFN, sensitization by the ABO blood system is common. However, this system has a benign character in the development of the disease, when compared to the Rh system, which has a higher prevalence, especially the D antigen, responsible for about 98 % of alloimmunization cases.[11]

Studies indicate that women with blood type O are more likely to develop the disease, as they produce a large fraction of IgG, which, as it is an immunoglobulin of low molecular weight, has the ability to cross the transplacental barrier. IgG binds to the antigens present on the surface of fetal erythrocytes which react with both A and B red blood cells causing hemolysis.[17,18] indicating that ABO incompatibility should not be overlooked.

In the current study, only 4 % of pregnant women confirmed the presence of RhD negative blood type, therefore, they had indication for immunoprophylaxis, which does not rule out the necessity of screening for non-RhD anti-erythrocyte antibodies. In the Brazilian population, the frequency of RhD negatives is estimated at 10–11 % and is associated with the most severe cases of the disease. Despite the severity, failure to perform antibody screening and apply prophylaxis with anti-D immunoglobulin is still observed. The reasons may be related to lack of immunoglobulin in the maternity ward, non-authorization of the pharmacy sector or even lack of information.[19]

Although cases are often associated with ABO and Rh system incompatibility, other blood groups may be involved in HDFN, such as Kell, Duffy, Kidd and MNS. Such systems are neglected in terms of prevention, although they are known to

Table 3 – Relationship between the number of correct answers to the questions about the hemolytic disease of the fetus and newborn and the socio-epidemiological variables and gestational profile in pregnant women receiving care at two municipal health units in Belém, Pará, Brazil.

Variable	0–4 correct answers Total=91		5–8 correct answers Total = 13	
	n	%	n	%
Level of education[a]				
Elementary School education	5	6	–	–
Incomplete high school education	11	12	–	–
Complete high school education	37	41	3	23
Incomplete higher education	14	15	1	8
Complete higher education	24	26	9	69
Family income[b]				
<1 minimum wage	33	36	1	8
Between 1 and 2 minimum wages	45	50	2	15
>2 minimum wages	13	14	10	77
Age group[c]				
<18 years	3	3	–	–
18–23 years	25	28	2	15
24–29 years	27	30	5	39
30–35 years	22	24	3	23
>36 years	14	15	3	23
Gestational age[d]				
First trimester (1–12 weeks)	15	17	–	–
Second trimester (13–26 weeks)	34	37	4	31
Third trimester (27–40 weeks)	42	46	9	69
Number of pregnancies[e]				
Primiparous	53	58	8	62
Multiparous	38	42	5	38

[a] p-value = 0.0456.
[b] p-value≤0.0001.
[c] p-value = 0.7596.
[d] p-value = 0.0855 by G test.
[e] p-value = 0.9400 by chi-square test.

cause mild, moderate or severe hemolysis. Thus, the erythrocyte antigens of these systems are rare in HDFN, but are present in alloimmunization, thus becoming a problem for sensitized pregnant women,[20] reinforcing the need to disseminate information about the disease among pregnant women and health professionals.

This was the first study carried out in the northern region of Brazil to evaluate the clinical management and knowledge of pregnant women about HDFN. In Brazil, data are limited; one study carried out in the city of São Paulo showed a lack of knowledge of pregnant women in respect to this subject and related matters, such as blood typing and the Rh factor. The findings suggested that lack of knowledge reduces as the level of education and monthly family income increases,[13] which corroborates the results of the current study, which showed a significant association between the number of correctly answered questions regarding knowledge and the schooling and family income variables.

Low education can be considered a risk factor, as it can favor non-adherence to treatment, due to the difficulty in reading and understanding the information, as well as limiting access to knowledge on specific topics, as demonstrated in a study that evaluated the level of knowledge of pregnant women on gestational diabetes.[21]

Regarding the pregnant women's socio-epidemiological and gestational profile, there was a predominance of pregnant women aged between 24 and 29 years, with complete high school education and who started prenatal care in the first trimester of pregnancy, corroborating maternal data from the Pará region obtained from the Live Births Information System in 2020. This database shows a higher frequency of women (53 %) aged 20–29 years, with 8 to 11 years of study (58 %) who attended pre-natal programs and whose participation was considered more than adequate in relation to its start and the number of consultations (at least six) (39 %) out of a total of 132,938 registered in the period.[22]

In addition, it is possible to observe that most of the evaluated pregnant women were in the third trimester of pregnancy. This could be an important factor to gain more information with the beginning of prenatal care at an appropriate time and adequate number of consultations however, this was not a confirmed hypothesis when evaluating the participants' level of knowledge about the disease.

On the other hand, most pregnant women were primiparous, contrasting with a study carried out on RhD alloimmunization with 289 pregnant women receiving care in the public health network of Rio de Janeiro, Brazil. This study evaluated the gestational profile of participants and found that the majority were multiparous and reached out to the referral center more often in the 3rd trimester, leading to a late diagnosis and failure to use immunoglobulin in a timely manner. This condition results in irreversible consequences such as fetal/neonatal death.[9]

When put together, the data indicate that prenatal care was adequate in the city of Belém in relation to the timing,

but the number of pregnancies did not influence knowledge about the disease.

Blood transfusion is considered a risk factor for sensitization in pregnant women, as the formation of immune complexes that lead to alloimmunization might occur. The literature points out that 20 % of women report having received blood transfusions unrelated to pregnancy in the course of their lives.[23] In the present study, most pregnant women reported not having had blood transfusions, which reduces the possibility of alloimmunization.

Regarding the clinical management of HDFN, most of the surveyed women carried out ABO and Rh blood typing during prenatal care, as recommended by the Brazilian National Health Service (SUS), which recommends blood typing from the first prenatal consultation. In cases of Rh-negative pregnant women and Rh-positive parents, an antibody screening should be requested monthly after 24 weeks to verify the possibility of prior sensitization. After laboratory identification of Rh negative patients with Rh positive partners (biological father), the application of anti-D immunoglobulin is indicated in the 28th week of pregnancy or up to 72 h after delivery.[10-12]

Most pregnant women did not receive antibody screening because they were Rh positive, therefore, they had no indication for the administration of anti-D vaccine, which is considered a limitation of this study as women who do not require vaccination do not require knowledge regarding this procedure and for this would not understand the purpose of the anti-D vaccine. Many believed that if the newborn is negative he would need the vaccine and even that the mother and the newborn must get the vaccine.

The findings of this research corroborate other studies that demonstrated failure in the management of prenatal care in several aspects, since the number of pregnant women who did not have enough knowledge about the disease was significant. Another investigation reported that from 50 to 70 % of pregnant women, especially those with alloimmunization, claimed to need more verbal information about the consequences of the disease for the fetus.[5] Furthermore, as a limitation of this study, it must be remembered that health units are all different and so pregnant women in different municipalities and states receive different information, contributing to disparities that can be minimized with health education programs.

Conclusion

The results showed that pregnant women have limited knowledge on the subject of HDFN especially those with less education and lower wages. Moreover, inadequate guidance about the disease in relation to the dissemination of information is lacking, reinforcing the importance of improving prenatal care and women's health care and the development of studies that strengthen relations between the academic community and society to promote health education.

Conflicts of interest

The authors declare no conflicts of interest.

Author contributions

A.M.S.; F.M.R.; J.N.G.S contributed substantially to the conception and design of the project, participated in data collection, analysis and interpretation, and also wrote the manuscript. L. C.P carried out a critical review of the intellectual content and final approval of the version to be published.

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